Remarks

Claims 25-37, 40-44, 47-51, 54-58, and 61-74 are pending in the instant application.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected of claims 25-37, 40-44, 47-51, 54-58 and 61-74 under 35 U.S.C. § 112, first paragraph, for lack of enablement. *See* Paper No. 9, page 3, section 6.1 and Paper No. 11182003, continuation sheet. The Examiner alleges:

> The instant application does not disclose how many samples were used to determine expression. If only one or a few samples for each tissue type were analyzed, there is a high probability for false-negative and false-positive results, which was demonstrated by Clarke et al. in the variability of expression of the PIP protein in both cancerous and normal tissues. There is no information in the specification as to how many tissue samples were analyzed or the degree of expression in cancer tissue relative to normal tissue. The art teaches that expression of genes in cancerous or normal tissue from different sources can be highly variable. Because of the lack of information on number of samples analyzed, the instant specification does not enable the use of the protein of SEQ ID NO:83 as a cancer marker, and the rejection is maintained.

Paper No. 11182003, continuation sheet.

Applicants respectfully disagree and traverse on the grounds that the Examiner failed to make a *prima facie* case for an enablement rejection. Applicants note that the standard for enablement is whether the experimentation needed to practice the invention is undue or unreasonable. *See* M.P.E.P. § 2164.01 (emphasis added). The disclosed utility acknowledged by the Examiner, the use of SEQ ID NO:83 as a cancer marker, contains within it a connotation of how to use and the art recognizes that standard modes of administration/use are known and contemplated. Indeed, Applicants have disclosed, for example in Example 22 of the specification, a method of determining abnormal levels of a polypeptide in a biological sample. Therefore, 35 U.S.C. § 112 is satisfied. *See* M.P.E.P. § 2164.01(c). It is not mentioned anywhere in the enablement section of the M.P.E.P. (M.P.E.P. § 2164) that a minimum number of samples be analyzed or disclosed for the enablement requirement to be satisfied. For this reason, Applicants maintain that establishing statistical certainty and/or disclosing sample numbers are not a requirement for patentability. *See* M.P.E.P. § 2107.03 (I), page 2100-43.

Applicants believe that the Examiner is questioning the credibility of the claimed invention as a cancer marker rather than its enablement as a cancer marker. The Examiner

states that "[c]ontrary to the Applicant's argument, the determination of a cancer marker must be based on studying results from a considerable number of patients and statistical analysis." *See* Paper No. 9, page 6, lines 19-21. This statement seems to cast doubt on the claimed invention's credibility, not whether the specification enables one of ordinary skill in the art to make and/or use the claimed invention. Nevertheless, the Examiner has admitted that, "there is no reason to doubt the assertion that the gene encoding the polypeptide could be used as a cancer marker and is therefore credible ...". *See* Paper No. 9, page 5, lines 4-5. The Examiner then alleges that the specification is insufficient to enable the use of the polypeptide. Applicants assert that the specification, as filed, would enable one of ordinary skill in the art to practice the invention without undue experimentation. *See*, for example, page 201, line 25 to page 205, line 2 and page 364, line 4 to page 365, line 5 of the specification. Indeed, the use of specific proteins as potential markers for cancer was well known in the art even prior to the effective filing date of the instant application. *See*, for example, Anisowicz *et al.* (1996) Mol Med 2(5):624-636, abstract only (Exhibit A).

The M.P.E.P. states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

M.P.E.P. § 2164.04, citing *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis added). Applicants assert that the claimed invention can be used as a marker for cancer. Combined with the state of the art at the time of filing and the disclosure in the specification, Applicants maintain that the application contains enabling disclosure.

However, the Examiner appears to question the objective truth of the Applicants' disclosure and cites the references of Ferrari *et al.* and Clark *et al.* In the Advisory Action, the Examiner states that these two references "were cited to demonstrate that even a relatively small number of patients or tissue or cell samples can be useful in establishing the potential as a cancer marker, but that expression can be highly variable." *See* Paper No. 11182003, page 2 (emphasis added). Regardless of variability of expression, the references cited by the Examiner conclude that the markers tested can be used as a cancer diagnostic. *See* Ferrari *et al.*, page 6 of 9, last paragraph, second sentence and Clark *et al.*, abstract, second to last sentence. Assuming *arguendo* that expression is highly variable for a cancer marker, this

does not prevent its use as a cancer marker. For example, even though PIP is expressed in normal and tumor tissue, the authors conclude PIP mRNA has potential as a marker for breast micrometastasis. *See* Clark *et al.*, page 1007, first column, last paragraph. Similarly, even if the protein of SEQ ID NO:83 is expressed in normal, non-diseased tissues, this still does not rule out its usefulness or reliability as a cancer marker. A cancer marker of low prevalence can still be deemed a useful cancer marker. Elevated levels of alpha-fetoprotein were demonstrated in a single patient to be indicative of ovarian endometrioid adenocarcinoma. *See* Maida *et al.* (1998) Gynecol Oncol 71:133-136, abstract only (Exhibit B).

Lastly, Applicants note, "determining enablement is a question of law based on underlying factual findings." *See* M.P.E.P. § 2164.01. Applicants reiterate that nowhere in either the M.P.E.P. or U.S. Code Title 35 does it state that statistical analysis/certainty is required for enablement or even patentability. Applicants believe that the Examiner has failed to establish a *prima facie* case of lack of enablement based on the state of the art and the disclosure of the specification at the time of filing. Accordingly, Applicants assert that the claims fully meet the enablement requirements of 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection of claims 25-37, 40-44, 47-51, 54-58 and 61-74 be reconsidered and withdrawn.

Conclusion

Applicants respectfully request the remarks of the present response be entered and made of record in the present application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination and/or allowance of this application.

Applicants believe that there are no fees due in connection with the filing of this paper. However, should a fee be due, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for any further extensions of time under 37 C.F.R. § 1.136, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: January 20, 2004

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KKH/JMM/JL/vr

1: Mol Med. 1996 Sep; 2(5): 624-36. Related Articles, Links

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A novel protease homolog differentially expressed in breast and ovarian cancer.

Anisowicz A, Sotiropoulou G, Stenman G, Mok SC, Sager R.

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BACKGROUND: Using differential display (DD), we discovered a new member of the serine protease family of protein-cleaving enzymes, named protease M. The gene is most closely related by sequence to the kallikreins, to prostate-specific antigen (PSA), and to trypsin. The diagnostic use of PSA in prostate cancer suggested that a related molecule might be a predictor for breast or ovarian cancer. This, in turn, led to studies designed to characterize the protein and to screen for its expression in cancer. MATERIALS AND METHODS: The isolation of protease M by DD, the cloning and sequencing of the cDNA, and the comparison of the predicted protein structure with related proteins are described, as are methods to produce recombinant proteins and polyclonal antibody preparations. Protease M expression was examined in mammary, prostate, and ovarian cancer, as well as normal, cells and tissues. Stable transfectants expressing the protease M gene were produced in mammary carcinoma cells. RESULTS: Protease M was localized by fluorescent in situ hybridization analysis to chromosome 19q13.3, in a region to which other kallikreins and PSA also map. The gene is expressed in the primary mammary carcinoma lines tested but not in the corresponding cell lines of metastatic origin. It is strongly expressed in ovarian cancer tissues and cell lines. The enzyme activity could not be established, because of difficulties in producing sufficient recombinant protein, a common problem with proteases. Transfectants were selected that overexpress the mRNA, but the protein levels remained very low. CONCLUSIONS: Protease M expression (mRNA) may be a useful marker in the detection of primary mammary carcinomas, as well as primary ovarian cancers. Other medical applications are also likely, based on sequence relatedness to trypsin and PSA.

PMID: 8898378 [PubMed - indexed for MEDLINE]

☐ 1: Gynecol Oncol. 1998 Oct;71(1):133-6.

Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Ovarian endometrioid adenocarcinoma with ectopic production of alpha-fetoprotein.

Maida Y, Kyo S, Takakura M, Kanaya T, Inoue M.

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alpha-Fetoprotein (AFP) is well known as a tumor marker of ovarian endodermal sinus tumor or embryonal carcinoma in gynecological malignancies. However, AFP production is extremely rare in ovarian epithelial cancers. Here we report a case of a 53-year-old woman with an AFP-producing ovarian endometrioid adenocarcinoma. The serum AFP level was elevated up to 2759 ng/ml preoperatively, with a subsequent decrease to the normal range after treatment. Histological examination of the tumor revealed a well-differentiated endometrioid adenocarcinoma with small foci of clear cell components. None of endodermal sinus tumor, hepatoid carcinoma, or embryonal carcinoma components were observed. Immunohistochemical analysis revealed that AFP was expressed in the cytoplasm of the endometrioid glandular lesions, but not in the clear cell components. This is probably the first case of a pure type of ovarian endometrioid adenocarcinoma with significant levels of AFP expression. Copyright 1998 Academic Press.

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